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(54) Title: METHODS OF IDENTIFYING COMPOUNDS THAT TARGET tRNA SPLICING ENDONUCLEASE AND USES OF SAID COMPOUNDS AS ANTI-PROLIFERATIVE AGENTS

(57) Abstract: The present invention relates to a method for screening and identifying compounds that modulate the activity tRNA splicing endonuclease. In particular, the invention provides assays for the identification of compounds that inhibit animalia tRNA splicing endonuclease. The methods of the present invention provide a simple, sensitive assay for high-throughput screening of libraries of compounds to identify pharmaceutical leads useful for treating and/or preventing cancer.



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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US04/09572

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : A01N 61/00; C12Q 1/00; G01N 33/566, 573 AND 574

US CL : 435/4, 6, 7.2, 7.21, 41, 69.2, 91.3, 183; 514/1, 2

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 435/4, 6, 7.2, 7.21, 41, 69.2, 91.3, 183; 514/1, 2

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Please See Continuation Sheet

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 6,446,032 B1 (SCHIMMEL) 03 September 2002, see entire patent document.	33, 34, 36-39, 53, 54
X — Y	WO 02/083837 A1 (ALMSTEAD) 24 October 2002, see entire document, especially the abstract, examples and claims.	33, 34, 36-39, 53, 54 1-32 and 40-51
X — Y	WO 02/083953 A1 (PTC THERAPEUTICS) 24 October 2002, see entire document, especially the abstract, examples and claims.	33, 34, 36-39, 53, 54 1-32, 40-51
Y	WANG, M.J. et al. Substrate Masking: Binding of RNA by EGTA-Inactivated Micrococcal Nuclease Results in Artifactual Inhibition of RNA Processing Reactions. Nucleic Acids Research, 1990, Vol. 18, No. 22, pages 6625-6631, see entire publication, especially the abstract, pages 6625-6626, bridging paragraph, page 6626, paragraph, 6, page 6627, paragraph 8.	1-34, 36-51, 53, 54
Y	LI, H. et al. Crystal Structure and Evolution of a Transfer RNA Splicing Enzyme. Science, April 1998, Vol. 280, No. 10, pages 279-284, see entire article.	1-34, 36-51, 53, 54



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T"

later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X"

document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y"

document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&"

document member of the same patent family

Date of the actual completion of the international search

04 April 2005 (04.04.2005)

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US04/09572

C. (Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	HYDE-DERUYSCHE, R. et al. Detection of Small-Molecule Enzyme Inhibitors with Peptides Isolated from Phage-Displayed Combinatorial Peptide Libraries. Chemistry & Biology, 2000, Vol. 7, pages 17-25, see entire article, especially the abstract, Table I and pages 23-24.	1-34, 36-51, 53, 54
Y	ABELSON, J. et al. tRNA Splicing. Journal of Biological Chemistry, May 1998, Vol. 273, No. 21, pages 12685-12688, see entire article.	1-34, 36-51, 53, 54
Y	TROTTA, C.R. et al. The Yeast tRNA Splicing Endonuclease: A Tetrameric Enzyme with Two Active Site Subunits Homologous to the Archaeal tRNA Endonuclease. Cell, June 1997, Vol. 89, pages 849-858, see entire article.	1-34, 36-51, 53, 54
Y	VAUGHAN, M.D. et al. Methionine In and Out of Proteins: Targets for Drug Design. Current Medicinal Chemistry, 2002, Vol. 9, No. 3, pages 385-409, see entire article.	1-34, 36-51, 53, 54
X	WO 01/25486 A1 (UNIVERSITY OF MEDICINE AND DENTISTRY OF NEW JERSEY) 12 April 2001, see entire document, especially the abstract, examples and claims.	33, 34, 36-39, 53, 54
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Y		1-32, 40-51

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US04/09572

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☒ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
Please See Continuation Sheet
3. ☒ Claims Nos.: 35 and 52
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
Please See Continuation Sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☒ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐

The additional search fees were accompanied by the applicant's protest.

☐

No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US04/09572

Continuation of Box II Reason 2:

Claims 35 and 52 are multiple dependent claims that depend from claims 33 and 34, which are dependent from claim 12, which is a multiple dependent claim. Thus a multiple dependent claim (i.e., claim 12) serves as a basis for claims 35 and 52, which are multiple dependent claims. Claims 35 and 52, therefore, are improper dependent claims, (see Rule 6.4 (a)).

BOX III. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I, claim(s) 1-32 and 40-51, drawn to methods for identifying a compound that modulates animalia tRNA splicing endonuclease activity.

Group II, claim(s) 33, 34, 36-39, 53, and 54, drawn to methods of preventing, treating, managing or ameliorating a proliferative disorder by administering an antiproliferative compound identified by the Group I method.

The inventions listed as Groups I and II do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: the methods of Groups I and II are distinctly different methods drawn to different method objectives. The antiproliferative compounds of Group II and derived from the Group I methods do not represent a "special" technical feature because antiproliferative compounds are known in the art. See e.g., WO 02/083953A1; WO 02/083837A1; and WO 01/25486A1.

Continuation of B. FIELDS SEARCHED Item 3:

WEST: PGPB, USPT, USOC, EPAB, JPAB, DWPI, TDBD.

STN: CAPLUS, EMBASE, BIOSIS, MEDLINE, WPIDS.